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Zinc acetate lozenges for treating the common cold: an individual patient data meta-analysis

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Key words:

Common cold; Meta-Analysis; Randomized controlled trials; Respiratory tract infections; Zinc acetate

AIMS

The aim of this study was to determine whether the allergy status and other characteristics of common cold patients modify the effects of zinc acetate lozenges.

METHODS

We had available individual patient data for three randomized placebo-controlled trials in which zinc acetate lozenges were administered to common cold patients. We used both one-stage and two-stage meta-analysis to estimate the effects of zinc lozenges.

RESULTS

The total number of common cold patients was 199, the majority being females. Eighty percent of them fell into the age range 20-50 years. One third of the patients had allergies. The one-stage meta-analysis gave an overall estimate of 2.73 days (95% CI 1.8 to 3.3 days) shorter colds by zinc acetate lozenge usage. The two-stage meta-analysis gave an estimate of 2.94 days (95% CI 2.1 to 3.8 days) reduction in common cold duration. These estimates are to be compared with the 7 day average duration of colds in the three trials. The effect of zinc lozenges was not modified by allergy status, smoking, baseline severity of the common cold, age, sex, or ethnic group.

CONCLUSION

Since the effects of zinc acetate lozenges were consistent between the compared subgroups, the overall estimates for effect seem applicable over a wide range of common cold patients. While the optimal composition of zinc lozenges and the best frequency of their administration should be further investigated, given the current evidence of efficacy, common cold patients may be encouraged to try zinc lozenges for treating their colds.

What is already known about this subject:

- Randomized trials have shown that zinc acetate lozenges shorten the duration of common cold episodes.
- One study found that the effect of zinc acetate lozenges was greater for patients with allergies.

What this study adds:

- The effect of zinc acetate lozenges is not modified by allergy, smoking, baseline common cold severity, age, sex, or ethnic group.
- The mean effect of 3 day reduction in common cold duration with zinc acetate lozenges is clinically relevant and appears widely applicable.

Introduction

Interest in zinc lozenges for treating the common cold arose when the cold symptoms of a 3-year-old girl with leukemia disappeared soon after she dissolved a therapeutic zinc tablet in her mouth instead of swallowing it as instructed [1]. The benefit seemed to be obtained from slowly dissolving the tablet in her mouth, which suggested that zinc might have local effects in the pharyngeal region. This observation led the girl's father to conduct the first randomized placebo-controlled trial on the effects of zinc lozenges on common cold patients. In that study, zinc gluconate lozenges shortened the duration of colds significantly [1].

Since then, a series of trials on zinc lozenges have been carried out but the results were variable [2-5]. The daily dosage of elemental zinc in the trials had a 7-fold variation, which explains much of the inconsistency in the study findings [2]. The composition of the lozenges also differed; some of them contained substances that bind zinc tightly, preventing the release of free zinc ions. The composition differences also explain divergent results [3-6].

A previous meta-analysis indicated that 5 low-dose trials of zinc lozenges (<75 mg/d zinc) uniformly produced no effect on the duration of colds. However, 3 high-dose (>75 mg/d) zinc acetate trials produced a 42% reduction in the duration of colds on average, and 5 high-dose zinc gluconate trials found a 20% reduction in cold duration on average [2]. Since acetate binds zinc ions less strongly than gluconate, zinc acetate has been proposed as the best salt for lozenges [4,5]. Although dissolving lozenges in the oro-pharyngeal region leads to the highest zinc levels in that anatomical region, a recent meta-analysis found no evidence that zinc acetate lozenges have less effect on nasal symptoms compared with cold symptoms that originate in lower anatomical regions [7]. Other systematic reviews on zinc and the common cold have been published [8-10], but some of them had methodological problems [11-13], and a Cochrane review was recently withdrawn [14].

Petrus et al. [15] reported that common cold patients who had positive skin testing for allergies were more responsive to the zinc acetate lozenges than those who were negative for allergies, but that association has not been analyzed in later studies. The effect of zinc lozenges might also be modified by smoking which influences the respiratory system, and by the severity of the common cold which reflects different levels of pathologic changes caused by the respiratory viruses. The goal of the present individual patient data (IPD) meta-analysis was to determine whether the efficacy of high-dose zinc acetate lozenges varies by the allergy status, smoking, baseline common cold severity or by demographic characteristics.

Methods

Selection of the trials

This meta-analysis was restricted to placebo-controlled trials on zinc acetate lozenges for patients with naturally acquired common cold infections, in which the elemental zinc dosage was >75 mg/d. We restricted the selection to high-dose trials, since previous analyses demonstrated the lack of effect of low doses of zinc, < 75 mg/day [2,4,5,10]. Previous searches of the literature [2,5,8-10] identified 3 trials that met our selection criteria [15-17]. These three trials are shown in Table 1 and further characteristics are shown in Supplement file 1. No additional zinc acetate lozenge trials were found by searching PubMed and Scopus using the free search terms "zinc" and "lozenge*" (June 16, 2016). The three datasets for this IPD meta-analysis were made available with the cooperation and collaboration of the authors of the three trials and the lead author. We did not use a protocol for this meta-analysis.

Outcome

The outcome in this meta-analysis was the duration of colds. Petrus et al. (1998) [15] reported both the mean duration of common cold symptoms and the duration of the longest cold symptom. We used the latter as the outcome for this analysis, since it is consistent with the outcome definition in the two studies by Prasad et al. [16,17].

Statistical methods

In checking of the IPD for the three studies, we confirmed that the effects of zinc lozenges in the IPD data were consistent with the published effects [15-17].

Pooling of the IPD was done by the one-stage and two-stage approaches. One-stage meta-analysis indicates that the pooled effect estimates are calculated directly from the IPD. Two-stage meta-analysis indicates that the effect estimates of the individual studies are first calculated from the IPD; thereafter, those study level estimates are pooled by standard meta-analysis methods. In some cases, the one-stage meta-analysis has greater statistical power and sometimes the two approaches lead to different conclusions [18].

We used the lmer procedure of the lme4 statistical package of R [19] for the one-stage meta-analysis. In the mixed models constructed with lmer, we used the study as the random variable for the zinc effect and also as an independent explanatory variable. The interaction between the zinc lozenge effect and each subgroup variable was calculated by first adding the zinc effect and the subgroup variable to the basic model, and thereafter adding their interaction term; the interaction between zinc and the subgroup variable was added as a random variable. The p-value for the interaction was calculated by using the likelihood ratio test.

In the two-stage pooling, we first used the lm procedure [19] to calculate the mean effects and the zinc-subgroup interactions separately in the three trials. Thereafter we pooled those effects by the metagen procedure of the meta package using the inverse-variance and random-effects options [19]. The p-value for the interaction was calculated from the z-value of the pooled interaction effect. We used the χ^2 test and the I^2 statistic to assess statistical heterogeneity among the three trials in the two-stage approach. A value of I^2 greater than about 70% indicates a high level of heterogeneity [20].

We used the difference in the duration of colds in days as the main measure of the zinc effect. However, since the distributions of viruses differ over time and the operational outcome definitions vary between trials, variation between studies is to be expected. Since relative effect adjusts for variation in the common cold duration in the placebo groups, we also calculated the overall effect of zinc in the percentage scale so that the duration of each placebo group was normalized to 100%. Thereby the difference between the zinc group and the placebo group directly gives the effect of zinc lozenges in percentages.

Our calculations are described in detail in Supplement file 2. Two-tailed p-values are used.

Results

Table 1 shows the distributions of the baseline variables of the three trials analyzed in this IPD meta-analysis. The trials had 199 common cold patients with the majority being females. Eighty percent of the common cold patients fell into the age range between 20 and 50 years. The majority was white, 23% were African Americans and 10% were of other ethnic origin. In the Petrus et al. study, all common cold patients were skin tested with 20 different allergy extracts including grasses, trees, and cat and dog dander, and 46% of the patients tested positive for allergies [15], see details in Supplement file 1. In their two trials, Prasad et al. asked about allergies with a questionnaire and 12% [16] and 20% [17] reported having allergies. Petrus et al. did not record information about smoking, whereas in the two studies by Prasad et al., a quarter of participants were smokers. All three studies were randomized, double-blind, placebo-controlled trials, and there were few drop-outs. Further details of the methodology of the three trials are described in Supplement file 1.

Petrus et al. instructed patients to dissolve in their mouth 1 lozenge every 1½ hour while awake on the first day, and then 1 lozenge every 2 hours on the following days; lozenges dissolved in about 15 minutes [15]. Prasad et al. instructed patients to dissolve 1 lozenge in their mouth every 2 to 3 hours while awake; their lozenges dissolved in about half an hour [5,16,17]. Elemental zinc dose varied between 80 and 92 mg/day in the three studies (Supplement file 1).

Table 2 shows the estimated effect of zinc acetate lozenges over all participants. The one-stage meta-analysis gives an estimate of a 2.73 day reduction in common cold duration and the two-stage meta-analysis gives an estimate of 2.94 days. These estimates are to be compared with the 7 day average duration of colds in the three trials (Table 2). The small difference between the two pooled estimates is explained by the substantially greater zinc effect and smaller SDs in the two small studies by Prasad et al. (N = 48 and N = 50), compared with the smaller effect and larger SD in the larger study by Petrus et al. (N = 101), see Table 2. The two-stage method gives a greater effect estimate for zinc lozenges since the total weight of the two studies by Prasad is 75%, although the number of participants is essentially equal with the Petrus et al. study [15], see forest plot in Supplement file 2.

The effectiveness of zinc acetate lozenges on the duration of colds on the relative scale is also shown in Table 2. One-stage IPD meta-analysis gave an estimate of 36% average reduction in common cold duration and the two-stage pooling gave an estimate of 40% average reduction in the duration of colds.

Table 3 shows the one-stage subgroup analyses of the zinc lozenge effects. The table shows the difference in the zinc lozenge effect between the complementary subgroups. The effect of zinc acetate lozenges was not modified by allergy, smoking, baseline severity of the cold, age, sex, or ethnic group. Age was analyzed as a continuous variable and no interaction with zinc effect was seen for that variable either. The two-stage approach gave similar results, see Supplement file 2. In the two-stage subgroup analysis, there was no heterogeneity in the interaction between the zinc effect and subgroups between the three trials.

Discussion

The effect of zinc acetate lozenges on the common cold was not modified by allergy, smoking, baseline severity of the common cold, age, sex, or ethnic group (Table 3). Our IPD meta-analysis does not support the earlier indication that zinc lozenges might be more effective for participants who have allergies [15].

Since no subgroup differences were found in the effect of zinc acetate lozenges, the overall estimates calculated in Table 2 are the most useful estimates for common cold participants comparable to the patients included in these three trials. Thus, given an average common cold duration of approximately one week (Table 2), zinc acetate lozenges may shorten common cold duration by an average of 3 days over various population groups.

A previous meta-analysis of the same three trials calculated that zinc acetate lozenges shortened the duration of colds on average by 42% [2]. That calculation was based on fixed-effect pooling of the reported study-level estimates. The current one-stage and two-stage IPD meta-analyses give similar overall estimates, though the current study calculated random-effects models.

Our meta-analysis was restricted to three studies with zinc acetate lozenges. Since there is evidence that acetate binds zinc ions less strongly than gluconate, zinc acetate has been proposed as a more suitable salt for lozenges than zinc gluconate [4,5]. Nevertheless, three studies with high doses of zinc as zinc gluconate also reported a statistically significant 21% to 48% reduction in the duration of colds [1,21,22]; see meta-analysis in [2]. The data of those old zinc gluconate studies were no longer available and we restricted our subgroup analysis to the three zinc acetate trials for which we had the IPD available.

Farr and Gwaltney [23] speculated that the apparent benefit of zinc gluconate lozenges reported by Eby (1984) [1] might have been explained by the bad taste of the lozenges. However, none of the three zinc acetate lozenge trials included in our meta-analysis showed that bad taste was a problem. There was no substantial difference between the zinc and placebo groups in the occurrence of adverse effects and only a few dropouts occurred [15-17]. In the most recent trial [17], a few patients identified the type of lozenge that they were administered, but when the analysis was restricted to those who remained blinded at the end of the trial, the efficacy of zinc lozenges was comparable to the efficacy for all participants.

Zinc doses of 100 to 150 mg/day have been administered to certain patient groups for months with few adverse effects [2,24-27]. Thus, it is unlikely that a zinc dose of some 80 mg/day for one to two weeks, starting soon after the first common cold symptoms, might cause long-term adverse effects. If a patient considers that the taste of the zinc lozenge is bad, he or she can discontinue using the lozenges, whereas other common cold patients may continue its use. Although the evidence is strong that properly formulated zinc lozenges can shorten the duration of colds, it appears that the majority of zinc lozenges on the market have either doses of zinc which are too low or contain substances that bind zinc, such as citric acid [5]. Therefore, the findings of this analysis should not be directly generalized to the wide variety of zinc lozenge formulations on the market.

In conclusion, our IPD meta-analysis found that the effect of zinc acetate lozenges on the duration of the common cold is not modified by allergy, smoking, baseline common cold severity, age, sex, or ethnic group. The calculated 3 day and 36% estimates for the reduction of common cold duration are substantial effects and worth utilizing by common cold patients. The optimal composition of zinc lozenges and the best frequency of their administration should be further investigated. Nevertheless, given the current evidence of efficacy and the low rate of adverse effects, common cold patients may be encouraged to try zinc acetate lozenges for treating their colds.

Supplement file 1: Description of the three studies included. See at the end of this manuscript.

Supplement file 2: Description of the statistical calculations. See at the end of this manuscript.

Conflicts of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributions of authors

AP, JTF, and EJP organized the three trials and collected the data that was analyzed in this study. HH planned and carried out this meta-analysis and wrote a draft manuscript. AP, JTF, and EJP participated in the revision of the manuscript. HH is the guarantor of the paper.

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Table 1.
Characteristics of trials

Characteristic	All participants	Petrus (1998) [15]	Prasad (2000) [16]	Prasad (2008) [17]
All participants	199	101	48	50
Intervention				
Zinc	102	52	25	25
Placebo	97	49	23	25
Age (y)				
median	27.0	22.0	37.0	34.5
range	17-61	18-54	18-61	17-60
Sex				
Male	82	47	18	17
Female	117	54	30	33
Allergy				
No	137	55	42	40
Yes	62	46	6	10
Ethnic group				
White	132	73	29	30
Black	47	15	16	16
Other	20	13	3	4
Smoker *				
No	70	-	35	35
Yes	28	-	13	15
Severity score of the common cold at the baseline				
Below median	102	57	23	22
Above median **	97	44	25	28

* The Petrus study (1998) [15] did not collect data on smoking.

** The common cold severity above median was ≥8 points in the Petrus study (1998) [15], ≥11 points in the Prasad study (2000) [16], and ≥8 points in the Prasad study (2008) [17], see Supplement file 1 for details.

Table 2. Effect of high-dose zinc acetate lozenges on common cold duration among all participants in the three trials included

	Duration of colds in the placebo group (days)		Effect of zinc on cold duration in absolute units (in days)		Effect of zinc on cold duration in relative terms (in %)	
	Mean	SD	Estimate (in days)	95% CI	Estimate (in %)	95% CI
Trials:						
Petrus 1998 [15]	7.1	3.9	-1.77	-3.1, -0.47	-25%	-44%, -6.7%
Prasad 2000 [16]	8.1	1.8	-3.61	-4.6, -2.6	-45%	-57%, -32%
Prasad 2008 [17]	7.1	1.3	-3.12	-3.8, -2.4	-44%	-53%, -34%
The 3 trials pooled:						
One-stage meta-analysis	7.3		-2.73	-3.3, -1.8	-36%	-45%, -24%
Two-stage meta-analysis	7.4		-2.94	-3.8, -2.1	-40%	-50%, -30%

Table 3. Difference in zinc acetate lozenge efficacy in subgroups: one-stage meta-analysis

Subgroup	No. patients	Difference in the subgroup effects		
		Estimate * (days)	95% CI (days)	Test of interaction (P)
Age	199	-0.5	-1.1, +0.06	0.2
Allergy				
No	137	ref.		
Yes	62	-0.9	-2.0, +1.1	0.11
Sex				
Male	82	ref.		
Female	117	+0.5	-0.9, +2.1	0.17
Ethnic group **				
White	132	ref.		
Black	47	-0.1	-2.0, +1.4	0.2
Smoker				
No	70	ref.		
Yes	28	-0.2	-1.5, +1.0	0.3
Severity of the cold at the baseline				
Below median	102	ref.		
Above median	97	+0.4	-2.0, +2.8	0.13

* The minus sign in the estimate for the difference indicates that on average zinc lozenges have a greater effect in the second subgroup compared with the zinc lozenge effect in the reference group, or in older participants; however, the P-values indicate that all differences are due to chance variation. The modifying effect of age on the zinc lozenge effect is calculated for a 10 year interval.
** Ethnic groups other than white or African Americans were excluded from this comparison.

Zinc acetate lozenges for treating the common cold: an individual patient data meta-analysis

Supplementary File 1 **version June 17, 2016**

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http://www.mv.helsinki.fi/home/hemila/
http://www.mv.helsinki.fi/home/hemila/Zinc.htm

This is additional material to a manuscript by Hemilä et al. (2016).

The tables in this document describes the selection of patients, the definition of outcomes, details of methods, and other essential characteristics of the three included trials.

Petrus (1998) [15]	http://www.currenttherapeuticres.com/article/S0011-393X%2898%2985058-3/abstract http://dx.doi.org/10.1016/S0011-393X(98)85058-3
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"The bottles of the zinc lozenges and placebo were sent by the manufacturer and each bottle was identical except a sequential number. At registration, after qualifying for the study each patient was given a bottle of 180 lozenges. At the conclusion of the study, when the diaries were assembled, the code for the bottles was sent by the manufacturer, and the patients were placed in the zinc or placebo category. Then the results were tabulated and the statistical analysis was undertaken" (Edward Petrus 24 March 2016).
Allocation concealment	Patients and personnel did not know to which group the patients were allocated.
Blinding of patients and personnel	Reported as double-blind, which implies that patients and personnel were blinded.
Blinding of outcome assessment	Blinded "subjects were also informed that they were required to rate and record their symptoms in a diary " (p. 598). "Subjects recorded their symptoms every day until their symptoms ceased (p. 598).
Losses to follow-up	1 patient was lost to follow-up.
Patients	Included in the analysis: 52 Zn and 49 placebo patients 47 M 54 F, mean age 26 yr (range 18 to 54 yr) **Patients** were recruited from the campus of the University of Texas through posted announcements **Exclusions:** serious illnesses, organ transplants, disability "This study was conducted during July and August 1997, when pollen was at its lowest level" (p. 598).
Common cold definition	Presence of 2 or more of the following 11 symptoms: nasal drainage, nasal congestion, cough, fever, myalgia, headache, sore throat, scratchy throat, hoarseness, sneezing, malaise (p. 598).
Delay between cold onset and treatment initiation	"97 of the 101 subjects started using zinc lozenges on the first day of enrollment in the study (4 started on day 2 of enrollment), but the dataset doesn't contain any information on the length of time between onset of symptoms and start of zinc therapy" (Kenneth Lawson, email 11 Dec 2014).
Outcome definition	**Two outcomes** were reported: **1)** mean duration of all observed cold symptoms of the individual **2)** duration of the longest-lasting common cold symptom.
Measurement of severity of the baseline cold	"Subjects were also informed that they were required to rate and record their symptoms in a diary at the same time each day. Symptoms [see the 11 symptoms above] were graded as follows: 0 = absent; 1 = mild (symptom is present but not particularly a discomfort); 2 = moderate (symptom is clearly evident and a discomfort); or 3 = severe (symptom is a serious problem and clearly evident and a discomfort)" (p. 598). Thus, the maximum of the scale was 33 points. The recorded level of severity at the baseline varied from 2 to 23 points, with the median at 7 points.
Intervention	Zn acetate: one lozenge contained **9 mg Zn** (p. 597). Placebo lozenges contained sucrose octaacetate. Patients were instructed to use 1 lozenge every 1½ hour while awake during day 0, then 1 lozenge every 2 hour while awake on following days. **"averaged 9.9 lozenges per subject per day as long as symptoms persisted"** (p. 599).

Daily Zn dose from the lozenges	**89 mg/d** = 9.9/d × 9 mg
Lozenges	"The lozenges with zinc contained 9 mg of zinc in a 2.7 g dextrose base" (p. 597). "To achieve masking, sucrose octaacetate (0.169 mg) was used in the placebo, and both the placebo and zinc lozenges were peppermint flavored. A review of subjects' diary entries revealed that 4 subjects noted a chalky taste, 4 experienced a metallic aftertaste, and 3 complained of an upset stomach; none of the subjects noted a bitter taste. Most subjects liked the peppermint flavor. " (p. 599). "The lozenges ... dissolved in the mouth in about 15 minutes" (p. 602). "Lozenges dissolved in about 15 min " (p. 31 on [8]). "The Petrus and Prasad compressed lozenges were designed by the present author and were identical in composition. In addition to ZA, they contained directly compressible (agglomerated) dextrose as the tablet base, glycerol mono-stearate (2.5% tablet weight) as tablet lubricant, stevia for added sweetness and peppermint oil for flavor, with the composition compressed to near maximal hardness for slowest dissolution. Those ingredients were chosen specifically because they do not react with iZn" (p. 31 in [8]). "Lozenges were small zinc acetate lozenges consisting of a dextrose tablet base, 2.5% glycerol monostearate lubricant, stevia and peppermint oil on silica gel compressed with a force sufficient to allow them to dissolve in 15 min in the human mouth" (p. 485 in [9]).
Mean and SD of the common cold duration	Calculated from the IPD data set (the same as reported in 1998): Zn: Mean duration of the longest-lasting symptom: **5.288 days (SD 2.569)** Placebo: Mean duration of the longest-lasting symptom: **7.061 days (SD 3.907).**
Allergy testing	"Because common colds and nasal allergies cause many of the same symptoms, skin tests were performed on each subject to determine whether allergies were present. All subjects were skin tested with 20 different allergy extracts, …The extracts included ragweed mix, burweed marsh elder, cedar elm, Bermuda grass, Johnson grass, perennial rye grass, mountain cedar (juniper), Virginia live oak, pecan, American elm, Alternaria alternata, Hormodenorum cladospo rioides, Helminthosporium sativum, cockroach mix (American and German), cat dander, dog dander, dust mite mix, Western ragweed, a negative control (diluent), and a positive control (histamine). After a 15- to 30- minute waiting period, the results of the skin test were measured and recorded. Itching, swelling, or redness at the site of allergy extract application indicated a positive reaction to the allergen. Forty-six subjects (46%) tested positive for allergies, and 55 (54%) were negative" (pp. 597-598).
Adverse effects	"Only 1 subject was lost to follow-up, and none of the remaining 101 subjects discontinued because of side effects from the lozenges. .. A review of subjects' diary entries revealed that 4 subjects noted a chalky taste, 4 experienced a metallic aftertaste, and 3 complained of an upset stomach; none of the subjects noted a bitter taste. Most subjects liked the peppermint flavor" (p. 599).

Prasad (2000) [16]	http://www.annals.org/content/133/4/245.1 http://dx.doi.org/10.7326/0003-4819-133-4-200008150-00035
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"A research consultant prepared the randomization code and the packages of medication. The packages were identical in appearance except for the randomization numbers. A research assistant who was blinded to treatment assignments distributed the study medication" (p. 246).
Allocation concealment	Patients and personnel did not know to which group the patients were allocated.
Blinding of patients and personnel	"A research assistant who was blinded to treatment assignments distributed the study medication" (p. 246).
Blinding of outcome assessment	Blinded "participants were asked to complete a daily log documenting the severity of symptoms" (p. 246).
Losses to follow-up	"Two persons in the placebo group dropped out on day 2. One of the two persons had a sore mouth, and the other developed an ear infection for which care was transferred to a physician outside of Detroit Medical Center" (Legend to Table 1, p. 247).
Patients	Included in the analysis: 25 Zn and 23 placebo patients 18 M 30 F, mean age 37 yr (SD 11 yr). **Patients** were students, staff, and employees at Wayne State University, Michigan, who were ≥18 yr. In general, subjects were recruited during fall and winter months. **Exclusions:** Pregnancy, a known immunodeficiency disorder, chronic illnesses, and previous use of zinc lozenges. Subjects with history of allergies were not excluded.
Common cold definition	Presence of 2 or more of the following 10 symptoms: cough, headache, hoarseness, muscle ache, nasal discharge, nasal congestion, scratchy throat, sore throat, sneezing, and fever (p. 246).
Delay between cold onset and treatment initiation	Inclusion required that the cold had lasted for **24 hours or less.**
Outcome definition	"Resolution of cold symptoms was defined as the resolution of all symptoms (a total symptom score of 0) or the resolution of all but one mild symptom (a total symptom score of 1)" (p. 246).
Measurement of severity of the baseline cold	"Participants were asked to complete a daily log documenting the severity of symptoms [see the 10 symptoms above] and the medications taken throughout the duration of the cold. Every day, the participants graded each symptom as 0 for none, 1 for mild, 2 for moderate, and 3 for severe. Total symptom scores were calculated by summing the scores " (p. 246). Thus, the maximum of the scale was 30 points. The recorded level of severity at the baseline varied from 2 to 26 points, with the median at 11 points.
Intervention	Zn acetate: one lozenge contained **12.8 mg Zn** (p. 245). Placebo lozenges contained sucrose octaacetate. patients were asked to dissolve 1 lozenge in their mouth every 2 to 3 hr while awake. **The reported mean number of lozenges used per day in the Zn group was 6.2** (p. 249).
Daily Zn dose from the lozenges	**80 mg/d** = 6.2/d × 12.8 mg

Lozenges	"Each zinc lozenge consisted of 42.96 mg of zinc acetate dihydrate, 6.0 mg of peppermint oil, 16.0 mg of silica gel, 4.0 mg of stevia extract powder , 3.8 g of directly compressible dextrose, and 100 mg of glycerol monostearate. Each lozenge contained 12.8 mg of zinc. Each placebo lozenge contained 0.25 mg of sucrose octaacetate, 6.0 mg of peppermint oil, 16.0 mg of silica gel, 3.9 g of dextrose DC, and 100 mg of glycerol monostearate. The placebo and zinc lozenges were identical in weight (4 g), appearance, flavor, and texture" (p. 246). "The Petrus and Prasad compressed lozenges were designed by the present author and were identical in composition. In addition to ZA, they contained directly compressible (agglomerated) dextrose as the tablet base, glycerol mono-sterate (2.5% tablet weight) as tablet lubricant, stevia for added sweetness and peppermint oil for flavor, with the composition compressed to near maximal hardness for slowest dissolution. Those ingredients were chosen specifically because they do not react with iZn [ionic zinc] . The slower dissolution of the 4-g size lozenges was an advantage over the smaller lozenges in terms of efficacy" (p. 31 on [8]). "Compressed with a force sufficient to allow them to dissolve in 30 min in the mouth" (p. 485 in [9]).
Mean and SD of the common cold duration	Calculated from the IPD data set (the same as reported in 2000): Zn group: mean cold duration: **4.480 days (SD 1.636)** Placebo group: mean cold duration: **8.086 days (SD 1.807)**
Maintenance of blinding	"Comparability in taste between zinc and placebo was tested in healthy volunteers. Ten participants were given a zinc lozenge and 10 received a placebo lozenge. One week later, the participants who received zinc were given placebo and those who received placebo were given zinc. At each visit, the participants filled out a questionnaire in which they were asked to guess whether they received a zinc or placebo lozenge. They had seven choices: certainly placebo, certainly zinc, do not know, possibly placebo, possibly zinc, probably placebo, and probably zinc. Volunteers who selected "certainly," "probably," or "possibly" and were correct about the type of lozenge they received were considered correct. We therefore categorized participants as "correct," "incorrect," or "do not know." We assessed the adequacy of blinding among study participants by administering the questionnaire used to assess comparability of taste in healthy volunteers. Participants filled out the questionnaire at the beginning and at the end of the trial" (p. 247). "Of 20 participants who received zinc, 5% [n=1]correctly guessed that they were receiving active therapy. Of 20 participants who received placebo, 10% [n=2] correctly guessed that they were receiving placebo. Therefore, participants did not correctly guess which type of lozenge they were receiving much better than by chance. In addition, at the beginning of the trial, 48% of zinc recipients and 26% of placebo recipients correctly identified the lozenges (P > 0.2). At the end of the study, 56% of zinc recipients and 26% of placebo recipients correctly identified the lozenges (P = 0.09). None of these percentages exceeded 50%, indicating that blinding was adequate at the outset and was maintained throughout the study" (p. 247-248).
Adverse effects	"Except for mouth dryness and constipation, no statistically significant side effects occurred in zinc recipients compared with placebo recipients" (p. 250).

Prasad (2008) [17]	http://jid.oxfordjournals.org/content/197/6/795 http://dx.doi.org/10.1086/528803
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"A research consultant prepared the randomization code and the packages of medication. The packages were identical in appearance except for the randomization numbers. A research assistant who was blinded to treatment assignments distributed the study medication " (p. 796).
Allocation concealment	Patients and personnel did not know to which group the patients were allocated.
Blinding of patients and personnel	"A research assistant who was blinded to treatment assignments distributed the study medication " (p. 796). "The clinical assistant who collected all of the clinical information and remained in touch with the subjects who were recruited for the study remained completely blinded regarding the contents of the zinc and placebo pills" (Ananda Prasad 15 Dec 2014).
Blinding of outcome assessment	Blinded patients completed daily logs.
Losses to follow-up	No drop outs.
Patients	Included in the analysis: 25 Zn and 25 placebo patients 16 M 34 F, mean age 35 yr (SD 14 yr) **Patients** were students, staff, and employees at Wayne State University, Michigan, who were ≥18 yr **Exclusions:** Pregnancy, any known immune deficiency disorder or chronic illness, and previous use of zinc lozenges.
Common cold definition	Presence of 2 or more of the following 10 symptoms: cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, and fever (p. 796).
Delay between cold onset and treatment initiation	Inclusion required that the cold had lasted for **24 hours or less.**
Outcome definition	"Resolution of cold symptoms was defined as the resolution of all symptoms (a total symptom score of 0) or the resolution of all but 1 mild symptom (a total symptom score of 1)" (p. 797).
Measurement of severity of the baseline cold	"Participants were asked to complete a daily log documenting the severity of symptoms [see the 10 symptoms above] ... the subjects graded each symptom as 0 for none, 1 for mild, 2 for moderate, or 3 for severe. Total symptom scores were calculated by summing the scores of the 10 symptoms for each day" (p. 796-797). Thus, the maximum of the scale was 30 points. The recorded level of severity at the baseline varied from 2 to 20 points, with the median at 8 points.
Intervention	Zn acetate: one lozenge contained **13.3 mg Zn** (p. 796). Placebo lozenges contained sucrose octaacetate. patients were asked to dissolve 1 lozenge in their mouth every 2 to 3 hr while awake. **The reported mean number of lozenges used per day in the Zn group was 6.9** (p. 799).
Calculation of the daily Zn dose from lozenges	**92 mg/d** = 6.9/d × 13.3 mg

Lozenges	“The lozenges were cherry oil–flavored Fast Dry zinc acetate lozenges, manufactured by F & F Foods (Chicago, IL). The active lozenges contained 13.3 mg of zinc as zinc acetate in a hard candy that contained 3.8 g of sucrose and corn syrup and that was prepared using the open-pot batch method, with the active ingredient added last. 100% of the zinc was available at physiologic pH 7.4 in positively charged, ionic form. The placebo lozenges were of identical composition, except that they contained 0.25 mg of sucrose octaacetate rather than the active ingredient, zinc. There were no fats, metal chelators, or other zinc ion– binding agents in either the active or placebo lozenges. The placebo and zinc lozenges were identical in weight, appearance, flavor, and texture and were supplied by George Eby” (p. 796).
Mean and SD of the common cold duration	Calculated from the IPD data set (the same as reported in 2008): Zn group: mean cold duration: **4.00 days (SD 1.04)** Placebo group: mean cold duration: **7.12 days (SD 1.26)**
Maintenance of blinding	“Comparability in taste between zinc and placebo was tested in the participants at the beginning and the end of the trial. The participants filled out a questionnaire in which they were asked to guess whether they had received zinc or placebo lozenges. They had 5 choices: certainly placebo, certainly zinc, do not know, probably placebo, and probably zinc. Subjects who selected certainly or probably and were correct about the type of lozenges they received were considered to be correct. We therefore categorized participants as correct, incorrect, or do not know” (p. 797). “In the zinc group at the beginning of the study, only 1 subject identified the lozenges as certainly zinc, and 2 subjects identified them as probably zinc. Thus, 3 (12%) of 25 subjects in this group were correct. At the end of the study, 2 (8%) were correct; 1 subject identified the lozenges as certainly zinc, and another subject identified them as probably zinc. In the placebo group at the beginning of the study, 1 subject said that the lozenges were certainly placebo, and another subject identified them as probably placebo. Thus, 2 subjects (8%) in this group were correct. At the end of the study, none of the subjects identified the placebo lozenge correctly” (p. 799).
Adverse effects	“Adverse effects of the zinc and placebo lozenges are compared in table 3. The zinc and placebo groups did not differ significantly in the incidences of any of the adverse effects, including diarrhea, constipation, sweet taste, sour taste, bitter taste, aftertaste, dry mouth, mouth irritation, or bad taste. None of the subjects complained of either abdominal pain or vomiting” (p. 799).

Zinc acetate lozenges for treating the common cold: an individual patient data meta-analysis

Supplementary File 2 **version June 17, 2016**

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http://www.mv.helsinki.fi/home/hemila/
http://www.mv.helsinki.fi/home/hemila/Zinc.htm (zinc and the common cold)

This is additional material to a manuscript by Hemilä et al. (2016)

Statistical analyses of the studies are described in this file. Subgroup analysis of allergy for Table 3 is shown as an example of the mixed model calculations for the subgroup analyses.
Table S1 shows the transformation of duration to the 100% scale
Table S2 shows two-stage analysis of subgroup differences in zinc lozenge effects.
The data set used in the study is printed at the end of this file.

This file contains:

Table S1. Normalization of the common cold duration to Placebo group = 100%

The values on the right hand side are used in in the calculation of the percentage effects of zinc acetate.

These values are calculated by dividing the figures on the left side by the mean common cold duration in the placebo group on the left side marked by yellow. Eg, Petrus (1998) zinc group: 5.29/7.06 = 0.7493 = 74.9%

This transformation leads to percentage scale so that all the differences between Zn and placebo groups are percentage effects.

Trial [ref]	Duration of colds (days)				Duration of colds (% of the placebo level)			
	Zn		Placebo		Zn		Placebo	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Petrus 1998 [15]	5.29	2.57	7.06	3.91	74.9	36.4	100	55.3
Prasad 2000 [16]	4.48	1.64	8.09	1.81	55.4	20.2	100	22.3
Prasad 2008 [17]	4.99	1.04	7.12	1.27	56.2	14.6	100	17.8

Above table shows the transformation of the mean duration in the three studies to the percentage scale.

In Table 2 of the paper, the calculation of zinc acetate lozenge effect is done using
the absolute scale of days (left-hand side of the table) and
the relative scale (% effect on duration; right-hand side of the above table).

On the absolute scale, the Petrus (1998) study found
an 1.77 day reduction in common cold duration (= 5.29 – 7.06 days).

On the percentage scale, the Petrus (1998) study found
an 25.1% reduction in common cold duration (= 74.9% – 100% = 5.29/7.06 -1).

The relative scale has the benefit of adjusting for baseline variations between the placebo groups. Nevertheless, the absolute duration of the colds was used in the IPD subgroup analyses.

Table S2. Difference in zinc acetate lozenge efficacy in subgroups: **Two-stage** meta-analysis

Subgroup	No. patients	Difference in the subgroup effects		
		Estimate * (days)	95% CI (days)	Test of interaction (P)
Age	199	-0.3	-0.7, +0.1	0.15
Allergy				
No	137	ref.		
Yes	62	-0.7	-2.0, +0.5	0.24
Sex				
Male	81	ref.		
Female	118	+0.3	-0.8, +1.4	0.6
Ethnic group **				
White	133	ref.		
Black	46	-0.04	-1.2, +1.1	0.9
Smoker				
No	71	ref.		
Yes	27	-0.2	-1.4, +1.0	0.7
Severity of the cold at the baseline				
Below median	102	ref.		
Above median	97	+0.3	-1.2, + 1.7	0.7

* The minus sign in the estimate for the difference indicates that on average zinc lozenges have a greater effect in the second subgroup compared with the zinc lozenge effect in the reference group, or in older participants; however, the P-values indicate that all differences are due to chance variation. The modifying effect of age on the zinc lozenge effect is calculated for a 10 year interval.
** Ethnic groups other than white or African Americans were excluded from this comparison.

Table 2 analyses: One-stage pooling

Effect on common cold duration in days

```
> All <- lmer(Duration ~ 0+ Study + Zinc + (Zinc-1|Study))
> summary(All)
Linear mixed model fit by REML ['lmerMod']
Formula: Duration ~ 0 + Study + Zinc + (Zinc - 1 | Study)

REML criterion at convergence: 939

Random effects:
 Groups   Name Variance Std.Dev.
 Study    Zinc 0.605    0.778
 Residual      6.577    2.564
Number of obs: 199, groups:  Study, 3

Fixed effects:
              Estimate Std. Error t value
StudyPetrus    7.210      0.349   20.67
StudyP2000     7.870      0.486   16.19
StudyP2008     7.029      0.470   14.97
Zinc          -2.730      0.587   -4.65

Correlation of Fixed Effects:
             StdyPt SP2000 SP2008
StudyP2000  0.078
StudyP2008  0.076  0.087
Zinc       -0.261 -0.299 -0.291
> confint(All)
Computing profile confidence intervals ...
              2.5 % 97.5 %
.sig01       0.00   1.75
.sigma       2.33   2.83
StudyPetrus  6.84   8.09
StudyP2000   6.72   8.36
StudyP2008   6.04   7.63
Zinc        -3.27  -1.84
```

Effect on common cold duration in percentages

```
> PctAll <- lmer(DurPerc ~  0 + Study + Zinc + (Zinc-1|Study))
> summary(PctAll)
Linear mixed model fit by REML ['lmerMod']
Formula: DurPerc ~ 0 + Study + Zinc + (Zinc - 1 | Study)

REML criterion at convergence: 1967

Random effects:
 Groups   Name Variance Std.Dev.
 Study    Zinc   67      8.19
 Residual      1284     35.83
Number of obs: 199, groups:  Study, 3

Fixed effects:
              Estimate Std. Error t value
StudyPetrus   102.45       4.78   21.44
StudyP2000     97.29       6.56   14.83
StudyP2008     97.68       6.35   15.37
Zinc          -36.15       7.05   -5.13

Correlation of Fixed Effects:
             StdyPt SP2000 SP2008
StudyP2000  0.113
StudyP2008  0.110  0.116
Zinc       -0.328 -0.344 -0.336
> confint(PctAll)
Computing profile confidence intervals ...
              2.5 % 97.5 %
.sig01        0.0   18.8
.sigma       32.4   39.4
StudyPetrus  96.2  113.5
StudyP2000   83.4  106.1
StudyP2008   84.2  106.4
Zinc        -44.5  -24.6
```

Table 2 analyses: Two-stage pooling: Effect on cold duration in days

Calculation of estimate and SD for the zinc lozenge effect:

```
> Petrus.lm    <- lm(Duration ~ Zinc, zincIPD[Study == "Petrus",])
> summary(Petrus.lm)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)    7.061      0.470   15.04   <2e-16 ***
Zinc          -1.773      0.654   -2.71    0.008 **

Residual standard error: 3.29 on 99 degrees of freedom
Multiple R-squared:  0.069,     Adjusted R-squared:  0.0596
F-statistic: 7.34 on 1 and 99 DF,  p-value: 0.00795

> P2000.lm <- lm(Duration ~ Zinc, zincIPD[Study == "P2000",])
> summary(P2000.lm)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)    8.087      0.359   22.55  < 2e-16 ***
Zinc          -3.607      0.497   -7.26  3.7e-09 ***

Residual standard error: 1.72 on 46 degrees of freedom
Multiple R-squared:  0.534,     Adjusted R-squared:  0.524
F-statistic: 52.7 on 1 and 46 DF,  p-value: 3.73e-09

> P2008.lm <- lm(Duration ~ Zinc, zincIPD[Study == "P2008",])
> summary(P2008.lm)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)    7.120      0.232   30.68  < 2e-16 ***
Zinc          -3.120      0.328   -9.51  1.3e-12 ***

Residual standard error: 1.16 on 48 degrees of freedom
Multiple R-squared:  0.653,     Adjusted R-squared:  0.646
F-statistic: 90.4 on 1 and 48 DF,  p-value: 1.3e-12
```

Pooling of the estimates calculated above:

```
> All.meta <- metagen(TE, seTE, studlab,data=subgroups[which(subgroups$Subgroup == "All"),],sm="MD")
> All.meta
                  MD         95%-CI %W(fixed) %W(random)
Petrus 1998 -1.77 [-3.06; -0.49]      14.9       25.0
Prasad 2000 -3.61 [-4.58; -2.63]      25.9       32.6
Prasad 2008 -3.12 [-3.76; -2.48]      59.2       42.4

Number of studies combined: k=3

                            MD         95%-CI      z  p-value
Fixed effect model   -3.05 [-3.54; -2.55] -12.05 < 0.0001
Random effects model -2.94 [-3.81; -2.07]  -6.64 < 0.0001

Quantifying heterogeneity:
tau^2 = 0.3546; H = 1.6 [1; 2.99]; I^2 = 60.9% [0%; 88.8%]

Test of heterogeneity:
     Q d.f.  p-value
  5.11    2   0.0777

Details on meta-analytical method:
- Inverse variance method
- DerSimonian-Laird estimator for tau^2
```

Table 2 analyses: two-stage pooling: Effect on cold duration in days

Heterogeneity between the three studies is not statistically significant, with P = 0.08

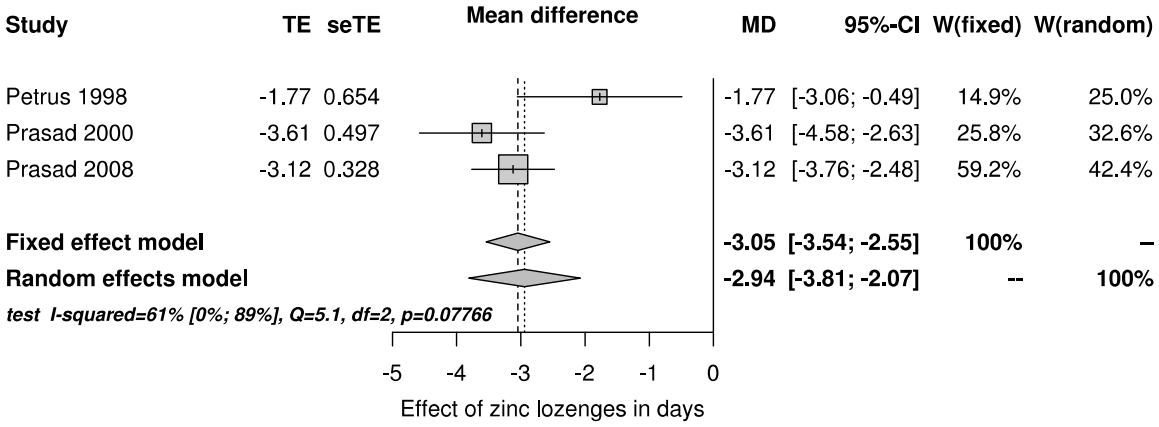

Table 2 analyses: Two-stage pooling: Effect on cold duration in percentages

Calculation of estimate and SD for the zinc lozenge effect:

```
> PercPetrus <- lm(DurPerc ~ Zinc, zincIPD[Study == "Petrus",])
> summary(PercPetrus)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   100.00       6.65   15.04   <2e-16 ***
Zinc          -25.11       9.27   -2.71    0.008 **

Residual standard error: 46.5 on 99 degrees of freedom
Multiple R-squared:  0.069,     Adjusted R-squared:  0.0596
F-statistic: 7.34 on 1 and 99 DF,  p-value: 0.00795

> PercP2000 <- lm(DurPerc ~ Zinc, zincIPD[Study == "P2000",])
> summary(PercP2000)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   100.00       4.43   22.55  < 2e-16 ***
Zinc          -44.60       6.14   -7.26  3.7e-09 ***

Residual standard error: 21.3 on 46 degrees of freedom
Multiple R-squared:  0.534,     Adjusted R-squared:  0.524
F-statistic: 52.7 on 1 and 46 DF,  p-value: 3.73e-09

> PercP2008 <- lm(DurPerc ~ Zinc, zincIPD[Study == "P2008",])
> summary(PercP2008)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   100.00       3.26   30.68  < 2e-16 ***
Zinc          -43.82       4.61   -9.51  1.3e-12 ***

Residual standard error: 16.3 on 48 degrees of freedom
Multiple R-squared:  0.653,     Adjusted R-squared:  0.646
F-statistic: 90.4 on 1 and 48 DF,  p-value: 1.3e-12
```

Pooling of the estimates calculated above:

```
> AllPerc.meta <- metagen(TE, seTE, studlab,data=subgroups[which(subgroups$Subgroup ==
"AllPerc"),],sm="MD")
> AllPerc.meta
                   MD          95%-CI %W(fixed) %W(random)
Petrus 1998 -25.1 [-43.3;  -6.94]      13.7       20.5
Prasad 2000 -44.6 [-56.6; -32.56]      31.1       34.5
Prasad 2008 -43.8 [-52.9; -34.78]      55.2       45.0

Number of studies combined: k=3

                            MD         95%-CI      z  p-value
Fixed effect model   -41.5 [-48.2; -34.8] -12.11 < 0.0001
Random effects model -40.2 [-49.9; -30.5]  -8.14 < 0.0001

Quantifying heterogeneity:
tau^2 = 33.1767; H = 1.35 [1; 2.48]; I^2 = 45% [0%; 83.7%]

Test of heterogeneity:
     Q d.f.  p-value
  3.64    2   0.1622

Details on meta-analytical method:
- Inverse variance method
- DerSimonian-Laird estimator for tau^2
```

Table 2 analyses: two-stage pooling: Effect on cold duration in percentages

Heterogeneity between the three studies is not statistically significant, with P = 0.16

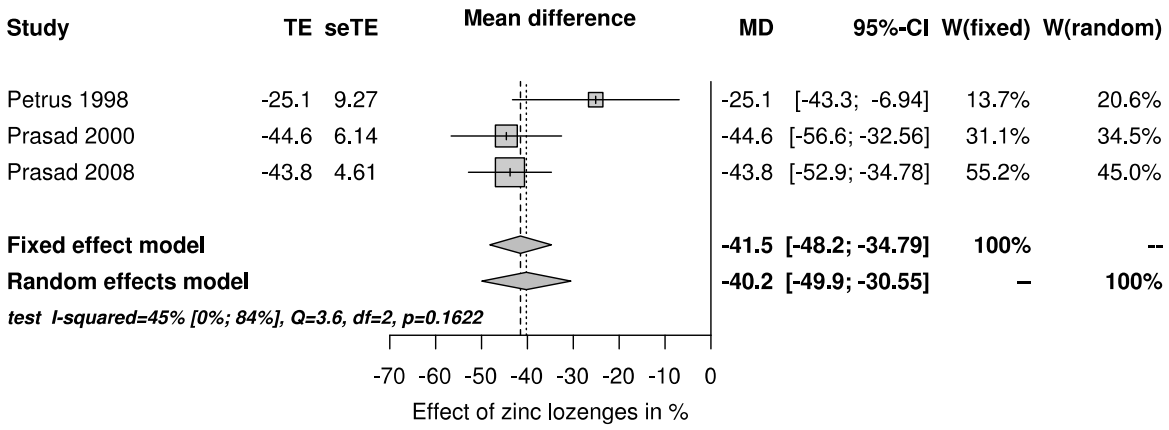

Table 3 analyses: One-stage pooling: Interaction between zinc lozenge effect and allergy status

```
  > AllerR2 <- lmer(Duration ~ Study + Study*Allergy + Zinc*Allergy + (Zinc-1|Study) +
        (Zinc:Allergy-1|Study) )
> summary(AllerR2)
Linear mixed model fit by REML ['lmerMod']
Formula: Duration ~ Study + Study * Allergy + Zinc * Allergy + (Zinc -
     1 | Study) + (Zinc:Allergy - 1 | Study)

REML criterion at convergence: 930

Random effects:
 Groups   Name         Variance Std.Dev.
 Study    Zinc         9.14e-01 9.56e-01
 Study.1  Zinc:Allergy 5.24e-14 2.29e-07
 Residual              6.59e+00 2.57e+00
Number of obs: 199, groups:  Study, 3

Fixed effects:
                     Estimate Std. Error t value
(Intercept)           6.737      0.464   14.52
StudyP2000            0.942      0.672    1.40
StudyP2008            0.165      0.654    0.25
Allergy               0.968      0.664    1.46
Zinc                 -2.488      0.707   -3.52
StudyP2000:Allergy    0.339      1.246    0.27
StudyP2008:Allergy   -0.158      1.047   -0.15
Allergy:Zinc         -0.892      0.825   -1.08

Correlation of Fixed Effects:
              (Intr) StP2000 StP2008 Allrgy Zinc   SP2000: SP2008:
StudyP2000   -0.609
StudyP2008   -0.627  0.428
Allergy      -0.646  0.371   0.373
Zinc         -0.283 -0.039  -0.011   0.206
StdyP2000:A  0.242 -0.401  -0.167  -0.377  0.009
StdyP2008:A  0.240 -0.164  -0.382  -0.348 -0.017  0.196
Allergy:Znc  0.389 -0.152  -0.143  -0.635 -0.315  0.093  -0.048
> confint(AllerR2)
Computing profile confidence intervals ...
                        2.5 % 97.5 %
.sig01                0.000   2.21
.sig02                0.000   1.66
.sigma                2.299   2.81
(Intercept)           6.345   7.97
StudyP2000           -0.863   2.13
StudyP2008           -1.479   0.60
Allergy              -0.561   1.97
Zinc                 -3.253  -1.54
StudyP2000:Allergy   -1.821   2.99
StudyP2008:Allergy   -2.265   1.80
Allergy:Zinc         -1.955   1.13

  > AllerR1 <- lmer(Duration ~ Study + Study*Allergy + Zinc+Allergy + (Zinc-1|Study) +
        (Zinc:Allergy-1|Study) )

  > lrtest(AllerR1,AllerR2)
Likelihood ratio test

Model 1: Duration ~ Study + Study * Allergy + Zinc + Allergy + (Zinc - 1 | Study) +
(Zinc:Allergy - 1 | Study)
Model 2: Duration ~ Study + Study * Allergy + Zinc * Allergy + (Zinc - 1 | Study) +
(Zinc:Allergy - 1 | Study)
  #Df LogLik Df Chisq Pr(>Chisq)
1  10   -466
2  11   -465  1  2.53       0.11
```

Table S2 analyses: Two-stage pooling: Interaction between zinc and allergy: interaction estimates in the three studies

```
> AllPe    <- lm(Duration ~ Zinc*Allergy, zincIPD[Study == "Petrus",])
> summary(AllPe)

Coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)     6.462      0.645   10.02   <2e-16 ***
Zinc           -1.082      0.888   -1.22     0.23
Allergy         1.278      0.941    1.36     0.18
Zinc:Allergy   -1.483      1.315   -1.13     0.26


Residual standard error: 3.29 on 97 degrees of freedom
Multiple R-squared:  0.0868,    Adjusted R-squared:  0.0586
F-statistic: 3.07 on 3 and 97 DF,  p-value: 0.0313

> AllP2000 <- lm(Duration ~ Zinc*Allergy, zincIPD[Study == "P2000",])
> summary(AllP2000)

Coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)     7.947      0.397   20.03   <2e-16 ***
Zinc           -3.556      0.536   -6.63    4e-08 ***
Allergy         0.803      0.952    0.84     0.40
Zinc:Allergy    0.306      1.591    0.19     0.85


Residual standard error: 1.73 on 44 degrees of freedom
Multiple R-squared:  0.549,     Adjusted R-squared:  0.518
F-statistic: 17.8 on 3 and 44 DF,  p-value: 1e-07

> AllP2008 <- lm(Duration ~ Zinc*Allergy, zincIPD[Study == "P2008",])
> summary(AllP2008)


Coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)     7.000      0.255   27.47   <2e-16 ***
Zinc           -3.000      0.370   -8.11    2e-10 ***
Allergy         0.750      0.637    1.18     0.25
Zinc:Allergy   -0.750      0.840   -0.89     0.38


Residual standard error: 1.17 on 46 degrees of freedom
Multiple R-squared:  0.663,     Adjusted R-squared:  0.641
F-statistic: 30.2 on 3 and 46 DF,  p-value: 6.09e-11
```

Table S2 analyses: Two-stage pooling: pooling of the interaction estimates: allergy

Zinc effect and allergy

No interaction between zinc effect and allergy (P = 0.24)
and no evidence of heterogeneity between studies (P = 0.7)

```
> ali <- metagen(TE, seTE, studlab,data=interactions[which(interactions$Subgroup == "Allergy"),],sm="MD")
> ali
                    MD         95%-CI %W(fixed) %W(random)
Petrus 1998 -1.483 [-4.06; 1.094]      24.2       24.2
Prasad 2000  0.306 [-2.81; 3.425]      16.5       16.5
Prasad 2008 -0.750 [-2.40; 0.896]      59.3       59.3

Number of studies combined: k=3

                              MD         95%-CI     z  p-value
Fixed effect model   -0.753 [-2.02; 0.515] -1.16   0.2443
Random effects model -0.753 [-2.02; 0.515] -1.16   0.2443

Quantifying heterogeneity:
tau^2 = 0; H = 1 [1; 1.9]; I^2 = 0% [0%; 72.3%]

Test of heterogeneity:
     Q d.f.  p-value
  0.75    2   0.6869

Details on meta-analytical method:
- Inverse variance method
- DerSimonian-Laird estimator for tau^2

>
```

Table S2 analyses: Two-stage pooling: pooling of the interaction estimates

Zinc effect and age

No interaction between zinc effect and age (P = 0.15)
and no evidence of heterogeneity between studies (P = 0.7)

```
> agi <- metagen(TE, seTE, studlab,data=interactions[which(interactions$Subgroup == "Age10"),],sm="MD")
> agi
                   MD          95%-CI %W(fixed) %W(random)
Petrus 1998 -0.243 [-1.719; 1.233]       7.4        7.4
Prasad 2000 -0.575 [-1.410; 0.260]      23.1       23.1
Prasad 2008 -0.204 [-0.686; 0.278]      69.5       69.5

Number of studies combined: k=3

                             MD          95%-CI     z  p-value
Fixed effect model   -0.293 [-0.694; 0.109] -1.43   0.1532
Random effects model -0.293 [-0.694; 0.109] -1.43   0.1532

Quantifying heterogeneity:
tau^2 = 0; H = 1 [1; 1.66]; I^2 = 0% [0%; 63.8%]

Test of heterogeneity:
    Q d.f.  p-value
 0.57    2   0.7502


>
```

Zinc effect and sex

No interaction between zinc effect and allergy (P = 0.6)
and no evidence of heterogeneity between studies (P = 0.6)

```
> sei <- metagen(TE, seTE, studlab,data=interactions[which(interactions$Subgroup == "Sex"),],sm="MD")
> sei
                   MD        95%-CI %W(fixed) %W(random)
Petrus 1998  1.374 [-1.21; 3.95]      17.0       17.0
Prasad 2000 -0.119 [-2.22; 1.98]      25.5       25.5
Prasad 2008  0.165 [-1.24; 1.57]      57.5       57.5

Number of studies combined: k=3

                            MD         95%-CI     z  p-value
Fixed effect model   0.298 [-0.765; 1.36] 0.549   0.5831
Random effects model 0.298 [-0.765; 1.36] 0.549   0.5831

Quantifying heterogeneity:
tau^2 = 0; H = 1 [1; 2.03]; I^2 = 0% [0%; 75.6%]

Test of heterogeneity:
    Q d.f.  p-value
 0.85    2   0.6525



>
```

Table S2 analyses: Two-stage pooling: pooling of the interaction estimates

Zinc effect and ethnic origin

No interaction between zinc effect and ethnic origin (P = 0.9)
and no evidence of heterogeneity between studies (P = 1.0)

```
> bli <- metagen(TE, seTE, studlab,data=interactions[which(interactions$Subgroup == "Black"),],sm="MD")
> bli
                    MD        95%-CI %W(fixed) %W(random)
Petrus 1998  0.2620 [-3.52; 4.04]      9.26       9.26
Prasad 2000 -0.0960 [-2.39; 2.20]     25.12      25.12
Prasad 2008 -0.0583 [-1.48; 1.36]     65.62      65.62

Number of studies combined: k=3

                              MD        95%-CI      z  p-value
Fixed effect model   -0.0381 [-1.19; 1.11] -0.065   0.9482
Random effects model -0.0381 [-1.19; 1.11] -0.065   0.9482

Quantifying heterogeneity:
tau^2 = 0; H = 1 [1; 1]; I^2 = 0% [0%; 0%]

Test of heterogeneity:
     Q d.f.  p-value
  0.03    2   0.9864
```

>

Zinc effect and smoking

No interaction between zinc effect and smoking (P = 0.7)
and no evidence of heterogeneity between studies (P = 0.7)

```
> smi <- metagen(TE, seTE, studlab,data=interactions[which(interactions$Subgroup == "Smoker"),],sm="MD")
> smi
                    MD        95%-CI %W(fixed) %W(random)
Prasad 2000 -0.4833 [-2.76; 1.79]      28.6       28.6
Prasad 2008 -0.0775 [-1.52; 1.36]      71.4       71.4

Number of studies combined: k=2

                             MD        95%-CI      z  p-value
Fixed effect model   -0.194 [-1.41; 1.02] -0.312   0.7549
Random effects model -0.194 [-1.41; 1.02] -0.312   0.7549

Quantifying heterogeneity:
tau^2 = 0; H = 1; I^2 = 0%

Test of heterogeneity:
     Q d.f.  p-value
  0.09    1   0.7674
```

>

Table S2 analyses: Two-stage pooling: pooling of the interaction estimates

Zinc effect and baseline common cold severity

No interaction between zinc effect and common cold severity (P = 0.7)
and no evidence of heterogeneity between studies (P = 0.2)

```
> sevi <- metagen(TE, seTE, studlab,data=interactions[which(interactions$Subgroup ==
"SeveBin"),],sm="MD")
> sevi
                   MD          95%-CI %W(fixed) %W(random)
Petrus 1998  2.196 [-0.372; 4.76]      15.5       22.4
Prasad 2000 -0.906 [-2.906; 1.09]      25.6       31.0
Prasad 2008  0.103 [-1.216; 1.42]      58.9       46.6

Number of studies combined: k=3

                            MD          95%-CI     z  p-value
Fixed effect model   0.170 [-0.842; 1.18] 0.329   0.7423
Random effects model 0.259 [-1.187; 1.70] 0.351   0.7257

Quantifying heterogeneity:
tau^2 = 0.7149; H = 1.33 [1; 2.42]; I^2 = 43.1% [0%; 82.9%]

Test of heterogeneity:
     Q d.f.  p-value
  3.51    2   0.1727




>
```

The following three pages show the data set that was analyzed in the study

Most of the variables are evident.

The definition of severity is described in Additional file 1 and the continuous scale was transformed to binary outcome “SeveBin” at the medians of the three studies.

Duration indicates the duration of common cold episodes
“DurPerc” is a transformed variable of duration so that:

all Petrus (1998) study duration values were divided by 7.0612 which is the placebo group mean common cold duration of that study,

all Prasad (2000) study duration values were divided by 8.0869 which is the placebo group mean common cold duration of that study,

all Prasad (2008) study duration values were divided by 7.12000 which is the placebo group mean common cold duration of that study,

“Study” variable indicates the studies, so that Petrus indicates the Petrus (1998) study [15], P2000 indicates the Prasad (2000) study [16], and P2008 indicates the Prasad (2008) study [17].

“NA” indicates not available.

```
zincIPD[,c(1:13)]
```

	ID	Age	Black	Sex	Allergy	Smoker	Severity	SeveBin	Zinc	Duration	DurPerc	Cured	Study
1	103	21	NA	0	0	NA	10	1	1	8	113.295	1	Petrus
2	105	18	0	0	1	NA	2	0	1	3	42.486	1	Petrus
3	106	40	1	1	0	NA	7	0	1	4	56.647	1	Petrus
4	107	37	0	0	1	NA	7	0	1	7	99.133	1	Petrus
5	109	42	0	1	0	NA	4	0	1	6	84.971	1	Petrus
6	111	21	0	1	0	NA	7	0	1	4	56.647	1	Petrus
7	115	22	0	0	1	NA	7	0	1	7	99.133	1	Petrus
8	119	21	0	1	0	NA	6	0	1	5	70.809	1	Petrus
9	121	22	0	0	1	NA	12	1	1	7	99.133	1	Petrus
10	122	20	0	1	1	NA	8	1	1	6	84.971	1	Petrus
11	123	30	0	1	0	NA	2	0	1	2	28.324	1	Petrus
12	125	22	0	1	0	NA	7	0	1	8	113.295	1	Petrus
13	127	22	0	0	1	NA	5	0	1	12	169.942	1	Petrus
14	128	20	0	0	1	NA	14	1	1	4	56.647	1	Petrus
15	129	22	0	0	1	NA	12	1	1	7	99.133	1	Petrus
16	132	25	1	1	0	NA	5	0	1	4	56.647	1	Petrus
17	133	20	0	0	0	NA	4	0	1	2	28.324	1	Petrus
18	137	24	0	0	1	NA	8	1	1	5	70.809	1	Petrus
19	139	24	1	1	0	NA	10	1	1	5	70.809	1	Petrus
20	141	23	1	1	0	NA	5	0	1	4	56.647	1	Petrus
21	142	19	NA	0	0	NA	2	0	1	7	99.133	1	Petrus
22	144	47	0	1	0	NA	4	0	1	11	155.780	1	Petrus
23	145	35	1	1	1	NA	14	1	1	3	42.486	1	Petrus
24	146	20	0	0	1	NA	7	0	1	6	84.971	1	Petrus
25	147	20	0	0	1	NA	5	0	1	3	42.486	1	Petrus
26	148	22	0	1	0	NA	6	0	1	4	56.647	1	Petrus
27	151	43	NA	1	0	NA	2	0	1	4	56.647	1	Petrus
28	153	22	0	0	1	NA	3	0	1	7	99.133	1	Petrus
29	155	21	0	0	1	NA	8	1	1	2	28.324	1	Petrus
30	158	20	0	0	0	NA	6	0	1	3	42.486	1	Petrus
31	159	50	1	1	0	NA	12	1	1	6	84.971	1	Petrus
32	161	21	0	1	0	NA	8	1	1	8	113.295	1	Petrus
33	163	41	1	1	0	NA	9	1	1	6	84.971	1	Petrus
34	165	31	1	1	0	NA	12	1	1	6	84.971	1	Petrus
35	166	24	0	1	1	NA	7	0	1	3	42.486	1	Petrus
36	167	21	1	0	0	NA	6	0	1	3	42.486	1	Petrus
37	168	28	NA	0	1	NA	9	1	1	8	113.295	1	Petrus
38	170	19	NA	0	0	NA	9	1	1	3	42.486	1	Petrus
39	171	36	0	1	0	NA	12	1	1	9	127.457	1	Petrus
40	174	41	NA	1	1	NA	4	0	1	3	42.486	1	Petrus
41	178	21	0	0	1	NA	3	0	1	4	56.647	1	Petrus
42	180	39	0	0	0	NA	7	0	1	2	28.324	1	Petrus
43	181	20	0	1	0	NA	6	0	1	4	56.647	1	Petrus
44	184	20	0	1	0	NA	5	0	1	2	28.324	1	Petrus
45	185	29	0	1	1	NA	7	0	1	3	42.486	1	Petrus
46	191	23	0	0	1	NA	8	1	1	8	113.295	1	Petrus
47	192	20	0	1	0	NA	10	1	1	10	141.618	1	Petrus
48	194	23	0	1	0	NA	11	1	1	5	70.809	1	Petrus
49	196	21	0	1	0	NA	8	1	1	11	155.780	1	Petrus
50	198	22	0	0	1	NA	9	1	1	6	84.971	1	Petrus
51	199	21	0	0	1	NA	5	0	1	3	42.486	1	Petrus
52	201	50	0	0	1	NA	5	0	1	2	28.324	1	Petrus
53	101	23	1	1	1	NA	20	1	0	2	28.324	1	Petrus
54	102	54	0	0	1	NA	10	1	0	2	28.324	1	Petrus
55	104	18	0	0	0	NA	14	1	0	7	99.133	1	Petrus
56	108	18	NA	1	1	NA	6	0	0	7	99.133	1	Petrus
57	110	21	0	0	1	NA	6	0	0	14	198.266	1	Petrus
58	112	21	0	1	0	NA	15	1	0	5	70.809	1	Petrus
59	113	21	0	0	0	NA	5	0	0	4	56.647	1	Petrus
60	114	28	0	1	1	NA	10	1	0	11	155.780	1	Petrus
61	116	42	0	1	0	NA	7	0	0	8	113.295	1	Petrus
62	117	21	0	1	1	NA	10	1	0	3	42.486	1	Petrus
63	118	22	0	1	0	NA	9	1	0	7	99.133	1	Petrus
64	120	29	0	1	0	NA	9	1	0	4	56.647	1	Petrus
65	124	22	0	1	0	NA	4	0	0	4	56.647	1	Petrus
66	126	52	0	0	0	NA	10	1	0	13	184.104	1	Petrus
67	130	22	NA	0	0	NA	10	1	0	4	56.647	1	Petrus
68	131	24	0	0	0	NA	9	1	0	6	84.971	1	Petrus
69	134	21	1	1	1	NA	7	0	0	13	184.104	1	Petrus
70	135	36	1	0	1	NA	5	0	0	5	70.809	1	Petrus
71	136	50	0	1	0	NA	6	0	0	5	70.809	1	Petrus
72	138	23	0	0	1	NA	4	0	0	7	99.133	1	Petrus
73	140	30	0	1	1	NA	13	1	0	15	212.428	1	Petrus
74	143	37	NA	1	0	NA	4	0	0	15	212.428	1	Petrus
75	149	24	1	0	1	NA	7	0	0	8	113.295	1	Petrus
76	150	24	0	1	0	NA	12	1	0	11	155.780	1	Petrus
77	152	29	1	0	1	NA	3	0	0	4	56.647	1	Petrus
78	154	34	NA	1	0	NA	13	1	0	5	70.809	1	Petrus
79	156	24	0	0	0	NA	7	0	0	6	84.971	1	Petrus
80	157	25	0	1	0	NA	10	1	0	3	42.486	1	Petrus

```
 81  160  20     0   1       1     NA       14       1    0        4  56.647     1 Petrus
 82  162  36    NA   1       1     NA        6       0    0       10 141.618     1 Petrus
 83  164  23     1   1       1     NA        6       0    0        4  56.647     1 Petrus
 84  169  19     0   1       0     NA        6       0    0        7  99.133     1 Petrus
 85  172  27     0   0       1     NA       11       1    0       12 169.942     1 Petrus
 86  173  31     0   1       1     NA       16       1    0        8 113.295     1 Petrus
 87  175  18     0   0       1     NA        7       0    0       14 198.266     1 Petrus
 88  176  22     0   0       0     NA        7       0    0        6  84.971     1 Petrus
 89  177  27     0   0       0     NA        7       0    0        2  28.324     1 Petrus
 90  179  32     0   0       0     NA        3       0    0        7  99.133     1 Petrus
 91  182  21     0   1       1     NA        4       0    0        5  70.809     1 Petrus
 92  183  21    NA   0       0     NA        4       0    0        6  84.971     1 Petrus
 93  186  18     0   1       0     NA        5       0    0        3  42.486     1 Petrus
 94  187  18     0   1       1     NA        2       0    0        4  56.647     1 Petrus
 95  188  26     0   1       0     NA       18       1    0        4  56.647     1 Petrus
 96  189  18     0   1       0     NA       17       1    0        5  70.809     1 Petrus
 97  190  20     0   0       0     NA        5       0    0       15 212.428     1 Petrus
 98  195  20     0   0       0     NA        7       0    0        6  84.971     1 Petrus
 99  197  21     0   0       1     NA       23       1    0       15 212.428     1 Petrus
100 200  28     0   1       1     NA       13       1    0        5  70.809     1 Petrus
101 202  28    NA   0       1     NA        8       1    0        6  84.971     1 Petrus

102 801  22     0   1       0      0        9       1    1        6  84.270     1  P2008
103 802  32     1   1       0      1       12       1    1        4  56.180     1  P2008
104 803  49     1   0       0      1        8       1    1        2  28.090     1  P2008
105 804  37     1   1       0      1       14       1    1        3  42.135     1  P2008
106 805  49     1   0       1      1       17       1    1        5  70.225     1  P2008
107 806  29     0   1       0      0       20       1    1        4  56.180     1  P2008
108 807  26    NA   1       0      0        4       0    1        5  70.225     1  P2008
109 808  22     0   1       0      0        7       0    1        4  56.180     1  P2008
110 809  19     0   1       0      0        6       0    1        3  42.135     1  P2008
111 810  38     0   0       0      0        9       1    1        3  42.135     1  P2008
112 811  19     0   1       0      0        8       1    1        5  70.225     1  P2008
113 812  18     0   1       0      0        6       0    1        4  56.180     1  P2008
114 813  20     0   1       0      1        9       1    1        3  42.135     1  P2008
115 814  25     1   1       0      0       11       1    1        4  56.180     1  P2008
116 815  56     0   1       1      0        9       1    1        4  56.180     1  P2008
117 816  59     1   1       1      0        4       0    1        2  28.090     1  P2008
118 817  26     0   0       0      0        7       0    1        5  70.225     1  P2008
119 818  23     1   1       1      0        4       0    1        5  70.225     1  P2008
120 819  39    NA   0       0      0       11       1    1        4  56.180     1  P2008
121 820  18     0   1       0      0       14       1    1        5  70.225     1  P2008
122 821  50     1   1       0      0        5       0    1        4  56.180     1  P2008
123 822  46     0   1       1      0        2       0    1        3  42.135     1  P2008
124 823  50     0   1       1      0       10       1    1        5  70.225     1  P2008
125 824  31     0   0       0      0        5       0    1        3  42.135     1  P2008
126 825  60     0   0       0      1        8       1    1        5  70.225     1  P2008
127 826  27     0   1       1      0        8       1    0        7  98.315     1  P2008
128 827  29    NA   1       1      0       11       1    0        9 126.404     1  P2008
129 828  50     0   0       0      1        3       0    0        7  98.315     1  P2008
130 829  45     1   1       1      1       15       1    0        7  98.315     1  P2008
131 830  23     0   0       0      0       19       1    0        6  84.270     1  P2008
132 831  42     1   0       1      1        8       1    0        8 112.360     1  P2008
133 832  48     1   0       0      1        7       0    0        6  84.270     1  P2008
134 833  19     0   1       0      0       13       1    0        7  98.315     1  P2008
135 834  56     1   1       0      0        8       1    0        8 112.360     1  P2008
136 835  23     0   1       0      0        6       0    0        6  84.270     1  P2008
137 836  21     0   1       0      1        6       0    0        8 112.360     1  P2008
138 837  20     0   0       0      0        8       1    0       10 140.449     1  P2008
139 838  40     0   1       0      0        6       0    0        7  98.315     1  P2008
140 839  45     1   1       0      1        4       0    0        4  56.180     1  P2008
141 840  53     1   0       0      1        6       0    0        8 112.360     1  P2008
142 841  47     0   1       0      0        5       0    0        9 126.404     1  P2008
143 842  39    NA   0       0      0        8       1    0        7  98.315     1  P2008
144 843  50     0   1       0      0        4       0    0        7  98.315     1  P2008
145 844  19     0   0       0      0        9       1    0        5  70.225     1  P2008
146 845  51     1   0       0      0        4       0    0        7  98.315     1  P2008
147 846  46     0   1       0      1       14       1    0        7  98.315     1  P2008
148 847  17     0   1       0      0        3       0    0        8 112.360     1  P2008
149 848  20     0   1       0      0        5       0    0        7  98.315     1  P2008
150 849  22     1   1       0      0        9       1    0        6  84.270     1  P2008
151 850  45     0   0       0      1        8       1    0        7  98.315     1  P2008

152 301  42     0   1       0      0        5       0    1        4  49.462     1  P2000
153 302  27     0   1       1      1       13       1    1        3  37.097     1  P2000
154 303  59     0   1       0      0        7       0    1        3  37.097     1  P2000
155 304  43     1   1       0      1       14       1    1        7  86.559     1  P2000
156 305  23     0   1       0      0        9       0    1        5  61.828     1  P2000
157 306  40     1   0       0      1       13       1    1        5  61.828     1  P2000
158 307  61     0   1       0      0       14       1    1        6  74.194     1  P2000
159 308  25     1   1       0      0       12       1    1        3  37.097     1  P2000
160 309  41     0   1       0      0        3       0    1        3  37.097     1  P2000
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161 310  19     0   1       0      1        6       0    1        3  37.097     1  P2000
162 311  42     0   1       0      0       12       1    1        2  24.731     1  P2000
163 312  59     1   1       0      0       18       1    1        7  86.559     1  P2000
164 313  28     0   0       0      0        5       0    1        6  74.194     1  P2000
165 314  38     0   1       0      0       10       0    1        6  74.194     1  P2000
166 315  24     0   0       0      0        6       0    1        4  49.462     1  P2000
167 316  36     0   1       1      0       13       1    1        8  98.925     1  P2000
168 317  32     0   0       0      0        2       0    1        5  61.828     1  P2000
169 318  33     0   1       0      0       26       1    1        2  24.731     1  P2000
170 319  34     0   0       0      0       11       1    1        4  49.462     1  P2000
171 320  31    NA   1       0      1       14       1    1        5  61.828     1  P2000
172 321  35     1   1       0      0       12       1    1        3  37.097     1  P2000
173 322  25    NA   0       0      0       13       1    1        5  61.828     1  P2000
174 323  38     0   1       0      0       11       1    1        6  74.194     1  P2000
175 324  33     0   1       0      0       11       1    1        4  49.462     1  P2000
176 325  43     0   0       0      0       11       1    1        3  37.097     1  P2000
177 326  42     0   1       1      0        6       0    0       10 123.656     1  P2000
178 327  29     0   0       1      1        6       0    0        8  98.925     1  P2000
179 328  40     1   0       0      1       11       1    0        9 111.290     1  P2000
180 329  32     0   1       0      0       11       1    0        9 111.290     1  P2000
181 330  42     1   0       0      1        6       0    0        7  86.559     1  P2000
182 331  54     1   1       0      0       11       1    0       12 148.387     1  P2000
183 332  22     1   1       0      0       14       1    0        9 111.290     1  P2000
184 333  37     1   0       0      1       10       0    0        7  86.559     1  P2000
185 334  29     0   1       0      0        6       0    0        5  61.828     1  P2000
186 335  52     1   0       0      1       11       1    0       12 148.387     1  P2000
187 336  24     0   0       0      0       15       1    0        6  74.194     1  P2000
188 337  56     1   1       1      1       11       1    0        9 111.290     1  P2000
189 338  43     1   0       0      0        6       0    0        7  86.559     1  P2000
190 339  54     1   0       0      1        9       0    0        8  98.925     1  P2000
191 340  18     0   0       1      0        6       0    0        8  98.925     1  P2000
192 341  38     0   1       0      0        6       0    0        8  98.925     1  P2000
193 342  42     0   0       0      0        8       0    0        9 111.290     1  P2000
194 343  33     1   1       0      0       11       1    0        6  74.194     1  P2000
195 344  40     1   0       0      1        7       0    0        8  98.925     1  P2000
196 345  52     0   1       0      0        3       0    0        8  98.925     1  P2000
197 346  31    NA   1       0      0       15       1    0        7  86.559     1  P2000
198 347  23     0   1       0      0        6       0    0        5  61.828     1  P2000
199 348  37     0   1       0      0        7       0    0        9 111.290     1  P2000
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